ISSN 1671-4083 Acta Pharmacol Sin 中国药理学报 2002 Apr; 23 (4): 289 - 295
http://www.chinaphar.com

Original Research

Effect of tachykinins on ascending and descending reflex pathway in rat small intestine[1]

R96 A

Andreas HAHN, Martin STORR[2], Hans-Dieter ALLESCHER
(*II Medizinische Klinik und Poliklinik der Technischen Universität München, 81675 München, Germany*)

KEY WORDS tachykinins; neurokinin-1 receptors; neurokinin-2 receptors; substance P

ABSTRACT

AIM: To examine the effect of tachykinins on the ascending reflex pathway in rat small intestine, we used different selective neurokinin (NK) receptor antagonists (RA): a) NK_1-RA: GR-82334 and CP-96.345, b) NK_2-RA: MEN-10.376 and L-659.877. The aim was further to investigate the effect of substance P (SP) on the ascending excitatory and descending inhibitory reflex pathway. **METHODS**: The whole segments of rat ileum (10 cm in length) were studied in an organ bath. Ascending contraction of circle muscle was elicited by anal electrical stimulation (3 Hz, 1 ms, 20 V) and measured as change of intraluminal pressure by a perfused manometric system 2 cm and 4 cm orad of the stimulation site. **RESULTS**: GR-82334 and CP-96.345 (NK_1-RA) caused a significant dose-related inhibition of the oral contraction at a distance of 4 cm: GR-82334 [area: $-10\ \% \pm 8\ \%$ (10 nmol/L); $-29\ \% \pm 10\ \%$ (1000 nmol/L). $P < 0.05$, $n = 10$], CP-96.345 [area: $-2\ \% \pm 6\ \%$ (0.1 nmol/L); $-14\ \% \pm 10\ \%$ (10 nmol/L). $P < 0.01$, $n = 8$], whereas the contractile response at a distance of 2 cm was unaltered ($n = 8$). In contrast, MEN-10.376 and L-659.877 (NK_2-RA) did not alter the amplitude or the area under the curve ($n = 10$). Neither the NK_1- nor the NK_2-receptor antagonists had a significant effect on the latency of the reflex response. SP showed a significant increase in the ascending contraction and the descending relaxation ($n = 6$, $P < 0.01$). **CONCLUSION**: These results demonstrate that blockade of NK_1-receptors decreases the oral reflex response. Latency of the reflex response remains unchanged, indicating that the effect is not due to an action on interneurons. NK_2-receptors do not take part in the ascending reflex in rat small intestine. SP increases the descending relaxant reflex response and ascending contraction.

INTRODUCTION

Tachykinins like substance P (SP) and neurokinin A (NKA) are present in and released from enteric neurons. NK_1-receptors have been located on neurons and interstitial cells of Cajal (ICC) in rat intestine and NK_2-receptors are located on muscle cells. Neurokinins, as part of the tachykinin family, are a group of five known peptides with the same C-terminal amino acid sequence (Phe-X-Gly-Leu-Met-NH_2) isolated from mammalian tissue[1]. They are named substance P (SP), neurokinin A (NKA), and neurokinin B (NKB) as well as neuropeptide K (NPK) and neuropeptide γ (NPγ), two extended forms of NKA. They are derived from the preprotachykinin A (SP, NKA, NPK, NPγ) and preprotachykinin B (NKB) gene[2-5]. Some of them (SP, NKA, NPγ) could be localized in and released from enteric neurons as neurotransmitters[6-8]. Today it is commonly accepted that tachykinins are a group of major excitatory transmitters in the intestine of motorneurons, interneurons, and afferent nerve fibers[6]. Some of them are co-localized (SP and NKA)[9]. Three distinct tachykinin receptors are named NK_1-, NK_2-, and NK_3-receptors. Further NK_2-receptor subtypes were postulated and classified into NK_{2A}- and NK_{2B}-receptor subtypes[10-13]. Neurokinin receptors were localized in

[1] Project supported by Deutsche Forschungsgemeinschaft, Bonn, Germany (DFG), Sonderforschungsbereich der Deutschen Forschungsgemeinschaft, Bonn, Germany (SFB), A1/245/8-1 and SFB-391-C5.
[2] Correspondence to Dr Martin STORR. Phn 349-89-4140-2258. Fax 349-89-4140-4932. E-mail martin.storr@lrz.tu-muenchen.de
Received 2001-08-23 Accepted 2002-01-11

ISSN 1671-4083 Acta Pharmacol Sin 中国药理学报 2002 Apr; 23 (4)
E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

smooth muscle cells in the intestine (NK_2-receptors)[14-17] and in neurons of the enteric nervous system (NK_1-receptors[12,18,19] and NK_3-receptors[18,20]). Recently NK_1 receptors were shown to be on interstitial cells of Cajal[12]. SP, NKA, and NKB preferentially bind at NK_1-, NK_2-, and NK_3-receptors, respectively[12,15]. But they are unselective and bind to all receptors with increasing concentration[15,21]. A oumber of different potent and selective NK_1- and NK_2-tachykinin receptor antagonists have been developed during the last few years[10,22]. GR-82334 and CP-96.345 are two NK_1-receptor antagonists, MEN-10.376 and L-659.877 are specific ligands to NK_2-receptors. In contrast there is a lack of specific NK_3-receptor antagonists. The proposed NK_3-receptor antagonist SR-14298 seems to exhibit its selective effects only in the guinea pig but have no discriminating activity in the rat (oral correspondence). A new receptor antagonist to NK_3-receptors in rat intestine is not available jet. Tachykinins show a potent effect on peristalsis in the small intestine, but less data is available on reflex pathway[14,15,17,23]. Therefore this study was performed to examine (1) the effects of different specific tachykinin NK_1- and NK_2-receptor antagonists; (2) the neurons involved; (3) the effect of substance P on the ascending and descending reflex response in rat small intestine.

MATERIALS AND METHODS

Experimental protocol Wistar male rats (300 – 400 g, Grade Ⅱ, Charles-River, Munich, Germany) were sacrificed using sodium pentobarbital intraperitoneally (80 mg/kg). The ileum was immediately removed and kept in oxygenated Krebs-Ringer buffer (KRB). An *in vitro* reflex model, a modification of the classical Trendelenburg preparation[24], was used to record ascending and descending reflex activity[25,26]. The whole segments of ileum (10 cm in length) were carefully dissected, and the mesenteric arcade was removed. The gut segments were placed in a 35 mL organ-bath filled with KRB, gassed with carbogen (95 % O_2, 5 % CO_2), and maintained at 37 ℃ by a thermostatic-water-bath. The oral and caudal end of the ileum were tied onto a polyvinyl tubing (outer diameter 4 mm) in such a way that the segment maintained its natural length. Intraluminal pressure, representative for circular muscle activity, was recorded by a perfused manometric system (Mui Scientific, Missisauga, Canada) measuring at 2 cm and 4 cm orad of the stimulation site[25]. Further force transducers (Grass, Quincy, MA, USA) were used to measure the effect of SP on the descending relaxation. Two of them were fixed 2 cm orad and 2 cm caudad from the stimulation site as described previously[26]. Two flat platinum electrodes (0.5 cm × 1.0 cm) were placed aborally (manometric system) and in-between (transducer system) the two recording sites, respectively. Then the preparation was allowed to equilibrate for at least 30 min. Contractile changes as well as latency between stimulation and contraction were measured and recorded using a Sensormedics R611 chart recorder (Sensormedics, Anaheim, CA, USA). Field stimulation impulses for neural responses were applied using a Grass S11 stimulator (Grass, Quincy, MA, USA), stimulating for 15 s at intervals of 2 min at standard parameters of 20 V pulse strength, 3 Hz pulse frequency, 2 ms pulse width. The stimulus signals were recorded simultaneously with the motility recording on the chart recorder using an A/C coupler (Beckman, Berlin, Germany). In the manometric system (Sigma scan, Jandel Scientific, USA) the oral contraction, the amplitude, the area under the curve, and the time of latency was recorded. In the system using the force transducers, the ascending contraction, the descending contractile response, and the descending relaxation were recorded by means of area under the curve.

Experimental design The gut segment was stimulated every 2 min, and periodic stimulation was maintained throughout the experiment. After an equilibration period of 30 min, a stable response to the electrical stimulation was established (identical contractions to at least 3 consecutive stimuli). Drugs were added 60 s after the last stimulation and before the next electrical stimulation. The substances were added to the bath in 35 μL volumes. For each concentration at least three reflex responses were elicited before the next concentration was applied. Appropriate control experiments were performed with vehicles to exclude unspecific effects. At the end of the experimental protocol, the buffer (KRB) was exchanged several times, and after a period of 15 min a control recording was performed.

Drugs Hexamethonium (HM), tetrodotoxin (TTX), and substance P (SP) were from Sigma (Irvine, UK); MEN-10.376, L-659.877, and GR-82334 from Research Biochemical International (RBI, Kiöln, Germany); CP-96.345 from Pfitzer GmbH (Karlsruhe,

Germany).

Krebs-Ringer buffer: Na^+ 138.68 mmol/L; Cl^- 122.61 mmol/L; HCO_3^- 22.14 mmol/L; glucose 11.11 mmol/L; K^+ 4.60 mmol/L; Mg^{2+} 1.25 mmol/L; Ca^{2+} 2.63 mmol/L; SO_4^{2-} 1.25 mmol/L; $H_2PO_4^-$ 1.16 mmol/L.

The drugs were dissolved in purified distilled water, stored at -20 ℃, and freshly resolved immediately before use and further diluted in KRB. The drugs were added in portions of 35 μL.

Statistics Data are expressed as $\bar{x} \pm s$ and n indicates the number of independent observations in different segments of small intestine. ANOVA analysis of variance with repeated measures and Bonferroni correction for multiple comparison were used to compare the mean values, and $P < 0.05$ was considered to be significant.

RESULTS

Characterization of the experimental system All motility responses caused by electrical field stimulation were abolished by tetrodotoxin (TTX) (300 nmol/L; oral contraction: $-96\ \% \pm 4\ \%$; caudal relaxation: $-94\ \% \pm 4\ \%$; caudal contractile response: $-100\ \% \pm 0\ \%$; $n=5$) as well as hexamethonium (0.1 mmol/L; oral contraction: $-100\ \% \pm 0\ \%$; caudal relaxation: $-90\ \% \pm 5\ \%$; caudal contractile response: $-100\ \% \pm 0\ \%$; $n=5$) demonstrating a neuronal and ganglionic transmission, which was consistent with the results reported previously[25].

Effects on NK_1-receptors GR-82334, a blocker of the NK_1-receptor, caused a significant inhibition of the amplitude ($P < 0.05$, $n=10$), the oral contraction and the area under the curve at a distance of 4 cm (Fig 1, Tab 1), whereas the response was not changed at a distance of 2 cm (Tab 1). The latency between onset of the stimulation and beginning of the contraction was unaltered at 2 cm and 4 cm (data for 4 cm: Fig 1, Tab 1) distance from the stimulation site.

CP-96.345, another NK_1-receptor antagonist, also caused a significant inhibition ($P < 0.05$, $n=8$), the area under the curve of the oral contraction at a distance of 4 cm (Fig 2, Tab 1), but was not altered at 2 cm distance. The amplitude and the latency were unaltered at 2 cm and 4 cm (data for 4 cm: Tab 1).

Effects on the ascending excitatory reflex pathway Using the force transducer system we investigated the effect of SP, a physiological agonist, which acts preferentially on NK_1-receptors, applied in a concentration of 30 nmol/L and 300 nmol/L. SP caused a significant increase of the ascending contraction (30 nmol/L: $+98\ \% \pm 14\ \%$; 300 nmol/L: $+182\ \% \pm 11\ \%$; $n=6$, $P<0.01$) and the descending contractile response (30 nmol/L: $+94\ \% \pm 20\ \%$; 300 nmol/L: $+255\ \% \pm 56\ \%$; $n=7$, $P<0.01$) (Fig 3, 4). Further an induction of spontaneous contractions and later an increase of the tone occurred, but these responses were

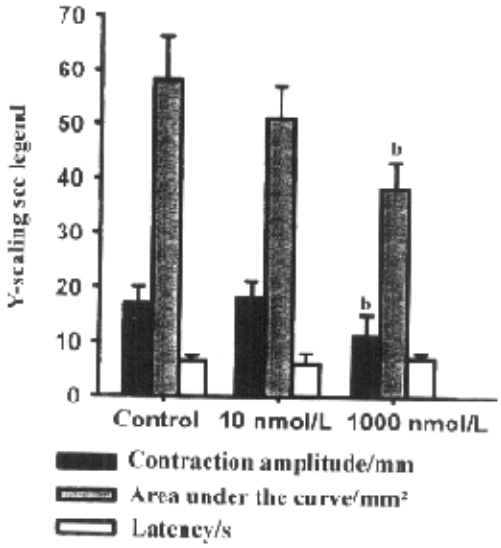

Fig 1. GR-82334 (10 nmol/L, 1000 nmol/L) reduced significantly the amplitude and the area under the curve of the ascending contraction at a distance of 4 cm. Latency between electrical field stimulation and contraction response was unaffected in rat small intestine. $n=10$. $\bar{x} \pm s$. $^bP<0.05$ *vs* control.

Tab 1. The effect of different neurokinin receptor antagonists on the oral contraction, area under the curve, and latency between onset of stimulation and begin of contraction. $\bar{x} \pm s$.

Group	Dose/ nmol·L^{-1}	n	Amplitude/ %	Area under the curve/ %	Latency/ %
GR-82334	10	10	6 ± 12	−10 ± 8	0 ± 20
	1000	10	−26 ± 10	−29 ± 10	28 ± 19
CP-96.345	0.1	8	4 ± 11	−2 ± 6	50 ± 33
	10	8	−2 ± 14	−14 ± 10	−33 ± 27
MEN-10.376	10	10	34 ± 23	12 ± 12	38 ± 37
	100	10	37 ± 29	14 ± 18	35 ± 38
	1000	10	−1 ± 16	4 ± 26	37 ± 37
L-659.877	10	10	−4 ± 7	0 ± 11	15 ± 21
	1000	10	4 ± 8	−6 ± 10	75 ± 35

ISSN 1671-4083 Acta Pharmacol Sin 中国药理学报 2002 Apr; 23 (4)
E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

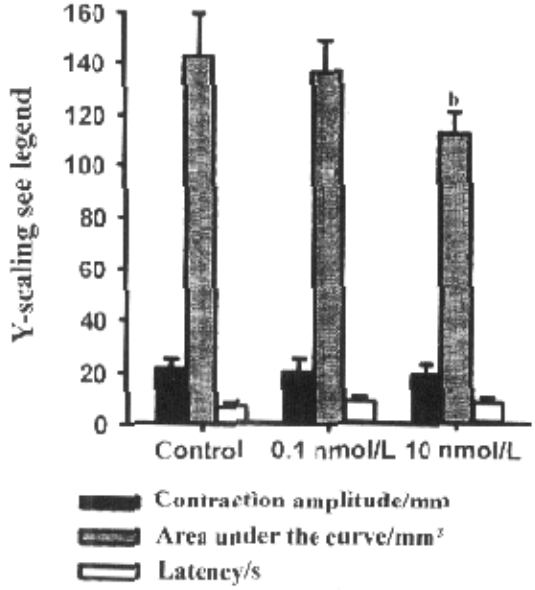

Fig 2. CP-96.345 (0.1 nmol/L, 10 nmol/L) reduced significantly the area under the curve of the ascending contraction at a distance of 4 cm. The amplitude of the contraction, as well as the latency between electrical field stimulation and contraction response of reflex pathway were not altered significantly in rat small intestine. $n = 8$. $\bar{x} \pm s$. $^bP < 0.05$ *vs* control.

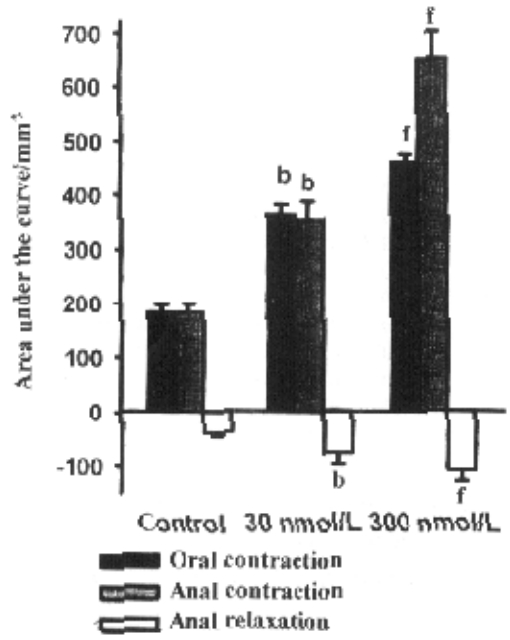

Fig 3. Substance P (30 nmol/L, 300 nmol/L) caused a significant increase of the ascending oral contraction, the descending caudal contractile response and the descending relaxation given as area under the curve in rat small intestine. $n = 7$. $\bar{x} \pm s$. $^bP < 0.05$ *vs* 300 nmol/L. $^fP < 0.01$ *vs* control.

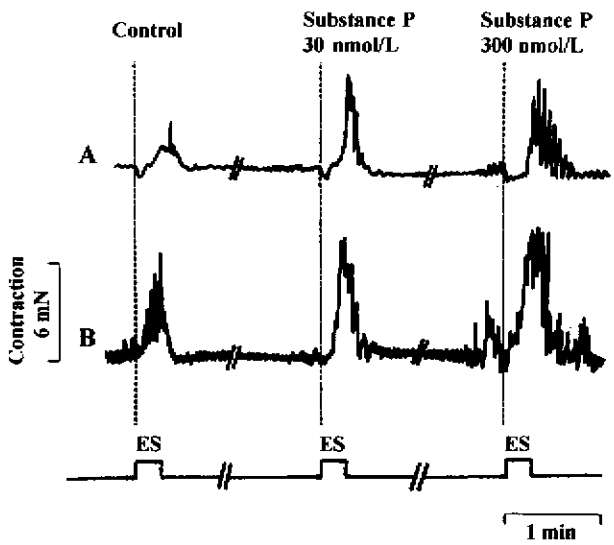

Fig 4. Representative trace of the increasing effect of substance P (30 nmol/L, 300 nmol/L) on the descending (A) contractile and ascending (B) contraction and relaxant reflex response in rat small intestine. ES: electrical field stimulation.

irregular and could therefore not be investigated systematically. They were not clear dose-dependent, but showed a trend towards higher concentrations (300 nmol/L). All effects were reversed completely after washout, what excluded a damage of the gut segment.

Effect on NK_2-receptors In contrast to the results from NK_1-receptor antagonists, MEN-10.376 (10 nmol/L, 100 nmol/L, 1000 nmol/L), a slightly specific NK_{2A}-receptor antagonist, did not alter the amplitude or the area under the curve ($n = 10$), neither at a distance of 4 cm (Tab 1) nor at a distance of 2 cm (data not shown). The latency was not changed by MEN-10.376 (Tab 1).

Similar results on the ascending reflex response in rat intestine were demonstrated by L-659.877, a specific NK_{2B}-receptor antagonist, at a dose of 10 nmol/L and 1000 nmol/L: contraction amplitude, area under the curve of the contraction, and latency were not altered, neither at a distance of 4 cm ($n = 10$, Tab 1) nor at 2 cm distance (data not shown).

Effect on the descending inhibitory reflex pathway Substance P used in a concentration of 30 nmol/L and 300 nmol/L caused a significant increase of the descending relaxation (30 nmol/L: +117 % ± 30 %; 300 nmol/L: +248 % ± 52 %; $n = 8$, $P < 0.01$) as shown by the original tracing in Fig 4 and the diagram in Fig 3.

DISCUSSION

Neurokinin receptors were shown by immunohistochemistry on neurons and interstitial cells of Cajal in rat intestine[18]. These results were confirmed by Western blot techniques[20]. NK_1-receptor stained neurons have recently been postulated to be interneurons, as most neurons did not leave the myenteric plexus. Some stained NK_1- and NK_2-neurons have the morphology of dogiel type Ⅱ neurons. Therefore these neurons were postulated to be sensory neurons. As demonstrated in our experimental system, SP, a known physiological excitatory neurotransmitter of motorneurons, interneurons and sensory neurons in the enteric nervous system, caused a significant increase of evoked contractions in reflex pathway in rat intestine at a concentration of 30 nmol/L and 300 nmol/L. SP is preferred but not highly specific to NK_1-receptors[10,21]. This is reflected by a variety of effects on motility: increase of evoked contractions and spasmogenic effects, induction of spontaneous contractions and increase of tone, especially at higher concentrations (300 nmol/L). Therefore it might be possible that more receptors could be involved. Also in other species SP is known to activate different neurokinin receptors[6].

Therefore to determine the receptors involved in rat myenteric plexus, we used in this study specific receptor antagonists which had been developed and used during the last years[11,21,22,27,28]. The excitatory effect of SP on reflex pathway in whole segments of rat intestine was confirmed by an inhibitory effect of two specific NK_1-receptor antagonists (GR-82334 and CP-96.345), indicating that SP acts via NK_1-receptors on the myenteric reflex pathway in rat intestine. Our results are consistent with the results of other reports in intestine, where SP was found to accelerate the transit of meal through the small intestine *in vivo*[6], which pointed at a possible altered reflex pathway. To examine the length of neurons involved we measured the reflex response at different distances. The inhibition of the oral contraction occurred at a distance of 4 cm from the stimulation site but was unaltered at 2 cm distance. Because of these results we postulate that SP acts on NK_1-receptors, most likely on longer ascending neurons in rat small intestine mediating the reflex response. Latency has been used as a parameter to measure effects on interneurons. This was shown previously in whole segments of rat intestine using different opioid agonists and antagonists which alter latency[29]. To investigate the kind of neurons involved we examined the effect of different tachykinin receptor antagonists on latency. NK_1-receptor antagonists could not change latency between onset of stimulation and the beginning of the reflex response, so that we speculate that interneurons are not involved. SP acts via NK_1-receptors on longer ascending motor neurons on the reflex pathway in rat intestine. Another mechanism is via release of histamine. It was shown that intestinal mast cells could be stimulated by SP to release histamine in rat intestine[30]. A close relationship between mast cells and nerve terminals containing SP is known[31,32] and the inhibitory effects of histamine H_1- and H_3-receptor blockers on the ascending reflex pathway have been demonstrated[26]. But this postulated mechanism of SP on histamine release is unlikely under our experimental conditions in rat intestine as the excitatory effect of SP could not be reduced by pre-treatment with pyrilamine (100 nmol/L) and clobenpropit (10 nmol/L) together (data not shown). NK_2-receptors do not take part in the ascending reflex pathway in rat intestine under our experimental conditions, as administration of both a specific NK_{2A}-(MEN-10.376)[21,27] and a NK_{2B}-(L-659.877)[11,21,28] receptor antagonist, did not change the electrical stimulated myenteric reflex pathway. Latency was unaffected after administration of both NK_2-receptor antagonists MEN-10.376 and L-659.877. A study[23] using the unspecific charcoal method showed an increase of transit via NK_2-receptors by application of [β-Ala^8]-NKA, an NK_2-receptor agonist. In these experiments it was not possible to determine the exact reason for the change of transit time. According to our data this could be an unspecific effect via ascending reflex pathway on NK_1-receptors or it might be due to a direct effect on the muscle layer. An effect via NK_2-receptors on the reflex pathway whereas seems to be unlikely. In experiments using isolated muscle strips of rat small intestine, an increase of contractions of the longitudinal muscle[17] as well as the circular muscle[14] was shown. The contractile response was postulated to be coupled with a Ca^{2+} signaling pathway[21].

While examinations were focused on the excitatory effects of tachykinins, no data exist about the effect on the descending inhibitory reflex pathway in rats. In this study SP is shown to increase clearly the descending relaxant reflex response. This result together with the demonstrated increase of contraction is in accordance with the concept of an possible accelerated propulsion caused

ISSN 1671-4083 Acta Pharmacol Sin 中国药理学报 2002 Apr; 23 (4)
E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

by tachykinins.

REFERENCES

1 Ersparmer V. The tachykinin peptide family. Trends Neurosci 1981; 4: 267 – 9.

2 Krause JE, Chirgwin JM, Carter MS, Xu ZS, Hershey AD. The rat preprotachykinin mRNAs encode the neuropeptides substance P and neurokinin A. Proc Natl Acad Sci USA 1987; 84: 881 – 5.

3 Krause JE, MacDonald MR, Takeda Y. The polyprotein nature of substance P precursors. Bioessays 1989; 10: 62 – 9.

4 Nakayama Y, Takano Y, Saito R, Kamiya H. Central pressor actions of tachykinin NK-3 receptor in the paraventricular nucleus of the rat hypothalamus. Brain Res 1992; 595: 339 – 42.

5 Stead RH, Tomioka M, Quinonez G, Simon GT, Felten SY, Bienenstock J. Intestinal mucosal mast cells in normal and nematode-infected rat intestines are in intimate contact with peptidergic nerves. Proc Natl Acad Sci USA 1987; 84: 2975 – 9.

6 Bartho L, Holzer P. Search for a physiological role of substance P in gastrointestinal motility. Neuroscience 1985; 16: 1 – 32.

7 Hurst SM, Stanisz AM, Sharkey KA, Collins SM. Interleukin-1beta-induced increase in substance P in rat myenteric plexus. Gastroenterology 1993; 105: 1754 – 60.

8 Nawa H, Hiose T, Takashima H, Inayama S, Nakanishi S. Nucleotide sequences of cloned cDNAs for two types of brain substance P precursors. Nature 1983; 306: 32 – 6.

9 Deacon CF, Agoston DV, Nau R, Conlon JM. Conversation of neuropeptide K to neurokinin A in vesicular colocalization of neurokinin A and substance P in neurons of the guinea pig small intestine. J Neurochem 1987; 48: 141 – 6.

10 Mussap CJ, Geraghty DP, Burcher E. Tachykinin receptors: a radioligand binding perspective. J Neurochem 1993; 60: 1987 – 2009.

11 Niel JP. Role of substance P in the nervous system control of digestive motility. Arch Int Physiol Biochem Biophys 1991; 99: A65 – A76.

12 Sternini C, Anderson K, Frantz G, Krause JE, Brecha N. Expression of substance P/neurokinin A-encoding preprotachykinin messenger ribonucleic acid in the rat enteric nervous system. Gastroenterology 1989; 97: 348 – 56.

13 Sternini C, Su D, Gamp D, Bunnett NW. Cellular sites of expression of the neurokinin-1 receptor in the rat gastrointestinal tract. J Comp Neurol 1995; 358: 531 – 40.

14 Maggi CA, Giuliani S. Role of tachykinins as excitatory mediators of NANC contraction in the circular muscle of rat small intestine. J Auton Pharmacol 1995; 15: 335 – 50.

15 Maggi CA, Giuliani S. Evidence that tachykinin NK-2 receptors modulate resting tone in the rat isolated small intestine. Br J Pharmacol 1996; 118: 1262 – 8.

16 Maggi CA, Giuliani S, Patacchini R, Turini D, Giachetti A. Tachykinin antagonists inhibit nerve mediated contractions in the circular muscle of the human ileum. Gastroenterology 1992; 102: 88 – 96.

17 Vigna SR, Bowden JJ, Mc Donald DM, Fischer J, Okamoto A, Mc Vey DC, *et al*. Characterization of antibodys to the rat substance P (NK-1) receptor and to a chimeric substance P receptor expressed in mammalian cells. J Neurosci 1994; 14: 834 – 45.

18 Mann PT, Southwell BR, Furness JB. Neurokinin 1 (NK_1) and neurokinin 3 (NK_3) receptor immunoreactive neurons in the rat gastrointestinal tract are putative intrinsic sensory neurons. In: AGA 1997; A1294.

19 Trendelenburg P. Physiologische und pharmakologische Versuche über die Dünndarmperistaltik. Naunyn-Schmiedebergs Arch Pharmacol 1917; 81: 55 – 129.

20 Grady EF, Baluk P, Böhm S, Gamp PD, Wong H, Payan DG, *et al*. Characterisation of antisera specific to NK_1, NK_2, NK_3 neurokinin receptors and their utilization to localize receptors in the rat gastrointestinal tract. J Neurosci 1996; 16: 6975 – 86.

21 Hellstrom PM, Murthy KS, Grider JR, Makhlouf GM. Coexistence of three tachykinin receptors coupled to Ca^{2+} signaling pathways in intestinal muscle cells. J Pharmacol Exp Ther 1994; 270: 236 – 43.

22 Maggi CA, Patacchini R, Rovero P, Giachetti A. Tachykinin receptors and tachykinin receptor antagonists. J Auton Pharmacol 1993; 13: 23 – 93.

23 Takeda Y, Krause JE. Pharmacological and molecular biological studies on the diversity of tachykinin NK-2 receptor subtypes in rat CNS, duodenum, vas deferens, and urinary bladder. Ann NY Acad Sci 1991; 632: 479 – 82.

24 Tramontana M, Maggi CA, Evangelista S. Spasmolytic effect of the NK-2 receptor-selective antagonist MEN 10,627 in rat small intestine. Jpn J Pharmacol 1994; 65: 281 – 3.

25 Allescher HD, Sattler D, Piller C, Schusdziarra V, Classen M. Ascending neuronal pathways in rat ileum *in vitro*-effect of capsaicin and involvement of nitric oxide. Eur J Pharmacol 1992; 217: 153 – 62.

26 Hahn A, Huber A, Neumayer N, Allescher HD. Effect of IL-1beta on the ascending and descending reflex in rat small intestine. Eur J Pharmacol 1998; 359: 201 – 9.

27 Maggi CA, Giuliani S, Ballati L, Lecci A, Manzini S, Patacchini R, *et al*. *In-vivo* evidence for tachykininergic transmission using a new NK-2 receptor-selctive antagonist, MEN 10.376. J Pharmacol Exp Ther 1991; 257: 1172 – 8.

28 Mc Knight AT, Maguire JJ, Elliott NJ, Fletsher AE, Foster AC, Tridgett R, *et al*. Pharmacological specifity of novel synthetic cyclic peptides as antagonists at tachykinin receptors. Br J Pharmacol 1990; 104: 355 – 60.

29 Allescher HD, Storr M, Brechmann C, Hahn A, Schusdziarra V. Modulatory effect of exogenous and endogenous opioids on the excitatory reflex pathway of the rat ileum. Neuropeptides 2000; 34: 62 – 8

30 Patacchini R, Astolfi M, Quartara L, Rovero P, Giachetti A, Maggi CA. Further evidence for the existence of NK_2 tachykinin receptor subtypes. Br J Pharmacol 1991; 104: 91 – 6.

31 Shanahan F, Denburg JA, Fox J, Bienenstock J, Befus D. Mast cell heterogeneity: effects of neuroenteric peptides on histamine release. J Immunol 1985; 135: 1331 – 7.
32 Stach W. Morphologische beziehung zwischen mastzellen und vegetativer endformation. Z Mikrosk Anat Forsch 1961; 67: 257 – 80.

速激肽对大鼠小肠上行及下行反射通路的作用[1]

Andreas HAHN, Martin STORR[2], Hans-Dieter ALLESCHER

关键词 速激肽类; 神经激肽-1 受体; 神经激肽-2 受体; P 物质

(责任编辑 韩向晖)